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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/530,580	10/10/2000	JEAN-PHILIPPE ROCHER	P19428	3575

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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,580	ROCHER ET AL.	
	Examiner	Art Unit	
	Binta M Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/7/00
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The restriction made in the office action dated 4/21/04 is dropped in light of applicant's comments and the search has been extended to the entire scope of the claims 1-22.

The objection to claim 18 made in the office action mailed 4/21/04 is dropped in light of applicant's amendments. The 112, first paragraph rejection of the terms "salt, hydrate thereof and a solvate" made beginning on page 8 of the office action mailed 4/21/04, is dropped in light of applicant's comments made 7/21/04. Part A of the 112, second paragraph rejection of claims 1-18, parts B and C of the 112, second paragraph rejection of claims 17-18 on page 15, and part D of the second paragraph rejection of claim 18 of the action mailed 4/21/04, are withdrawn in light of applicants amendments. The 112, first paragraph enablement rejection of radicals X, Y, and R4 and R5 made in the office action mailed 4/21/04 is modified.

(new objections)

Claim 2 is objected to. In claim 2, line 9, page 5 of the claims, the phrase "one substituents" is grammatically incorrect. The phrase should be amended to "one substituent".

(new rejections)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is also not established in the art to utilize pharmaceutical compositions to prevent diseases.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 1-22 is that novel compounds act as a ligand for the sigma 2 receptor/binding site and as medicaments comprising said compounds as an active ingredient.

The State of the Prior Art

The sigma receptor/binding site of the brain has been identified as an important target for the development of the antipsychotic drugs that are free from the side affects of currently available antipsychotic drugs having antagonistic activity on the dopamine

D2 receptor, See page 1 of the specification, lines 6-9. The pharmacological significance, distribution, and functions of the sigma 2 binding site is relatively uncertain in the art, since a selective agent has not been available for this site, although recent studies have revealed that the sigma 2 site plays a role in controlling functions for the ileum. See page 3 of the specification, lines 1-7. Benzimdazolemethyl piperidine derivatives have been disclosed in WO 87/02359, WO 8702035, WO/8702666 and US Patent No. 4215119, See page 3 of the specification, lines 20-21. But none of these publications have the benzothiazoline ring and have not been examined for their affinity for the sigma binding site. See page 3 of the specification, lines 27-28. There is no prior art disclosing the prevention of the said diseases or conditions with the sigma ligands.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since the pharmacological significance, distribution, and functions of the sigma 2 binding site is relatively uncertain in the art. The contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face. Moreover, there is no prior art disclosing the prevention of the said diseases or conditions.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compound of claim 1 and the binding of the instant compounds to the Sigma-2 receptor, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of Sigma-2 in the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Moreover, the specification fails to show:

*A method to determine the subjects that would certainly suffer from the said conditions or diseases

*A method showing the treatment that the said subjects need to undergo in order to prevent the said conditions or diseases

*Any data showing a follow up of the said subject already treated for a considerable amount of time in order to support the argument that the said subjects are no longer at any risk from suffering from the said diseases or conditions

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of claim 1 can bind to Sigma –2 receptors. However, the specification fails to provide guidance as

to whether the diseases disclosed as Sigma-2-mediated diseases, require the binding of sigma 2- ligands to the sigma-2 receptor for treatment of the claimed diseases. The applicant only provides binding assays for the instant compounds on the sigma-2-receptor; however, does not examine the pharmacological effects of these compounds on any of the diseases disclosed.

The presence or absence of working examples

There are no working examples for any diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease. Also, the specification fails to provide working examples as to how the disclosed diseases can be treated by the binding of instant compounds to the sigma-2 binding site, i.e. again, there is no correlation between the diseases listed and binding of the instant compounds to the Sigma-2 receptor site. The binding of the instant compounds on other sigma binding sites such sigma binding site 1 or 3 also have not been examined.

The breadth of the claims

The breadth of the claims is that the compound of claim 1 can treat any disease, caused or promoted by the nerve controlling function of a sigma ligand.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which disclosed diseases would be benefited by the binding of the instant compounds to the Sigma-2 receptor and would furthermore then

have to determine whether the claimed compounds would provide treatment of the disease by the binding of the instant compounds to sigma 2 receptor.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the prevention or treatment of any disease caused or promoted by the nerve controlling function of a sigma ligand. As a result necessitating one of skill to perform an exhaustive search for which Sigma-mediated diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which Sigma-mediated diseases can be

treated by the compound encompassed in the instant claims, with no assurance of success.

(old rejections)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, lines 9-10, page 3 of the amendment response filed 4/21/04, the phrase "together with other intervening atoms" is unclear. What other intervening atoms are the applicants claiming? Are these atoms within the heterocyclic ring?

B. Claim 17 is indefinite because it is not written in the proper format for a pharmaceutical composition claim. By definition, a pharmaceutical composition claim must contain a reference to a pharmaceutically acceptable, inert carrier.

(new rejections)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 1, lines 11-12, page 4, and all other occurrences throughout the claims 1-22, the term "substituted" is unclear . What substituents are the applicant claiming? In claim 1, line 6, and all other occurrences throughout the claims 1-22, the phrase "substituted or unsubstituted carbamoyl group, an acyl group" is redundant. A carbamoyl group is an acyl containing group. What other acyl groups are the applicant claiming?

B. In claims 1-22, the phrase "together with other intervening atoms" is unclear. What other intervening atoms are the applicants claiming? Are these atoms within the heterocyclic ring?

C. Claims 2, 3, and 5 recite the limitation "substituted phenyl group" –"the substituent is at least one substituents selected from the group consisting of a halogen atom, an alkyl group, a halogenated alkyl group, an alkoxyl group, a halogenated alkoxyl group, cyano group and a substituted or unsubstituted aminosulfonyloxygroup)"" in lines 9-11. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "X is a p-fluorophenyl group" in 2, page 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation "X is a p-fluorophenyl group" in 2, page 7. There is insufficient antecedent basis for this limitation in the claim. Claim 12 recites the limitation "X is a p-fluorophenyl group" in 2, page 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "X is a p-fluorophenyl group" in 2, page 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 recites the limitation "X is a p-fluorophenyl group" in 2, page 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "X is a p-fluorophenyl group" in 2, page 8. There is insufficient antecedent basis for this limitation in the claim.

D. In claim 19, line 1, page 8 of the claims, the phrase "sigma ligand" is indefinite. It is unclear if the sigma ligand being claimed is different from the instant compounds being claimed, is comprised of more than one compound, and is capable of binding to other sigma binding sites other than the sigma 2 binding site. The term "comprising" also renders this claim indefinite. The term "comprising" denotes that a mixture of two or more chemical species exists. It is unclear as to whether or not the sigma ligand is one compound, or is comprised of other compounds in addition to an instant compound of the formula I. If the sigma ligand is only one compound, then the language "comprising" is inappropriate. Does the sigma ligand comprise more than one compound, and if so what are the other compounds? If the sigma ligand comprises more than one compound, then this claim must be written in the appropriate format for a pharmaceutical composition claim with reference to an inert carrier.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17-18, 20-22 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

A method for the therapeutic treatment or prevention of a disease caused or promoted by nerve controlling function of a sigma ligand with the instant compounds as

well as a composition for the therapeutic treatment or prevention of a disease caused or promoted by nerve controlling function of a sigma ligand are not specific, credible, or substantial utilities. To overcome or avoid this rejection, the applicant must disclose a real-world use for the agonist, such as a believable assertion that it would have a pharmaceutical use. Since the fact pattern fails to establish definitively, what disease, , would be treatable by the compound, the claimed treatment and composition does not encompass a specific, substantial, and credible utility. Further studies are needed to elucidate the relation between the physiological function of sigma receptor and psychiatric diseases by the use of sigma receptor ligands and molecular techniques. See CA 137:57627.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

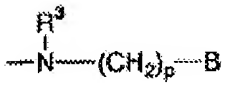
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A method for the therapeutic treatment or prevention of a disease caused or promoted by nerve controlling function of a sigma ligand with the instant compounds as well as a composition for the therapeutic treatment or prevention of a disease caused or promoted by nerve controlling function of a sigma ligand is not adequately described in

terms of real world uses such as actual diseases treated. Further, the method and composition requires treatment of diseases that have not been disclosed.

Therefore, the fact pattern indicates that the artisan was not in possession of the claimed method of use. In the absence of some understanding of the diseases to be treated and which, if any agonists could be sued to treat said disease, the artisan would not have accepted that the applicant was in possession of the claimed method. No in vivo test data confirms that the compounds in controlling the function of a sigma receptor 2 site are able to treat actual diseases claimed. A variety of physical characteristics was not obtained for the instant compounds where the Z radical is



that would distinguish these compounds from other similar molecules. A mere assertion that some molecule exists which may be an agonist for a particular receptor is not sufficient by these standards. In order to fufill the Written Description requirement for a receptor agonist claim, a few examples of agonists and a specific description of common features will be required.

The IDS filed 8/7/00 has been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
November 15, 2004

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600